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The effect of the NMDA receptor blocker, dextromethorphan, on cribbing in horses

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Abstract

Stereotypic cribbing in horses is thought to involve excess dopaminergic activity within the striatum. Various models of stress-induced stereotypies including cribbing in horses postulate that stress stimulates the release of endorphins, triggering the release of striatal dopamine. Dopamine in turn activates basal ganglia motor programs, reinforcing behavior via a reward mechanism. Furthermore, the release of dopamine by endorphins has been shown to depend on activation of NMDA receptors. In the present study, horses identified as cribbers and volunteered by their owners were treated with the NMDA receptor antagonist dextromethorphan (DM). When DM was administered via jugular injection (1 mg/kg), eight of nine horses responded with reductions in cribbing rate (CR) compared to baseline, and cribbing was suppressed completely for a period of time in almost half of the horses tested. © 2001 Elsevier Science Inc. All rights reserved.

Keywords: Stereotypic cribbing; Horses; NMDA receptor antagonist; Dextromethorphan

1. Introduction

Cribbing in horses has been described as a stereotypic behavior akin to obsessive compulsive disorders in humans (Shuster and Dodman, 1998). It is a repetitive behavior in which a horse grasps a ledge or rail with its teeth and then contracts its ventral neck muscles to retract the larynx caudally producing an influx of air into the pharynx (Dodman et al., 1987; McGreevy et al., 1995). Owners often find this behavior disturbing, although the actual physical toll of cribbing on horses appears to be minor (Cooper and Mason, 1998).

Treatment of cribbing by means of physical restraint and aversion therapy has met with little success because treated horses often continue to crib at some level (McGreevy and Nicol, 1998). Pharmacological treatments aimed specifically at the neurotransmitter systems underlying the pathology have targeted both the serotonergic and opioid systems (Dodman et al., 1987; Nurnberg et al., 1997). Oral stereotypies in rats induced by the administration of morphine were completely blocked by MK-801, a non-competitive NMDA receptor blocker, suggesting a role for glutamate (Livezey et al., 1995). The putative involvement of NMDA receptors in cribbing provides an additional neural pathway to be explored for the purpose of developing new treatments. Dextromethorphan (DM), the active ingredient in most cough medicines, is a non-competitive NMDA antagonist that is relatively inexpensive and has few toxic side effects. In pilot studies, two horses with other compulsive behaviors (self-directed biting and compulsive stall walking) showed temporary complete suppression of the behaviors after the injection of DM (unpublished results). The aim of the current study was to follow-up on the promising results of these earlier case studies.

2. Materials and methods

Horses identified as stereotypic cribbers were recruited through recommendations from equine veterinarians practicing in eastern Massachusetts. Nine horses of various breeds were used in the study. Their ages ranged from 4 to 15 years; six were geldings, and three were mares (Table 1). All horses wore cribbing straps that were removed prior to testing. The baseline cribbing rate

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Table 1
Description of cribbing horses

Horse	Breed	Age (year)	Weight (lb)	Sex
Snoopy	Pony	4	830	gelding
Chester	Quarterhorse	14	1000	gelding
Judd	Trakhener	15	1200	gelding
Lucky	Hanoverian	4	1270	gelding
Petey	Welsh Cobb	7	760	gelding
Cinnamon Buns	Pony	12	550	gelding
Nechima	Trakhener Cross	6	1210	female
Cameo	Hanoverian Cross	13	1210	female
Orangina	Oldenburger	7	1125	female

(CR) for each horse was measured following an intravenous (iv) injection of 10 ml of saline. The cumulative number of crib bites was counted for 60 min using a hand tally. Immediately following this control period, each horse was given an injection of DM (1 mg/kg iv) into the jugular vein, and cribbing behavior was tallied for an additional hour.

From these observations, CRs were determined as crib bites/min over each 60-min period. The mean control CR for all nine horses was compared to the mean post-treatment CR using a paired two-tailed Student's *t* test for significance of difference. In addition, to express the efficacy of DM treatment, the % maximum efficacy was calculated for each horse using the formula:

$$[(\text{Baseline CR} - \text{treatment CR})/\text{Baseline CR}] \times 100.$$

3. Results

The baseline CRs of the horses ranged from 1 to 8 bites/min with a mean ± S.E. CR of 4.4 ± 0.8 crib bites/min (Table 2). Following treatment with DM, the mean ± S.E. CR for the 60-min period fell to 2.3 ± 0.8 crib bites/min, a 48% decrease in frequency (P=.01).

Table 2
The effect of DM on CR

	CR (bites/min)		
Horse	10-ml Saline	1-mg/kg DM	% Maximum efficacy
Snoopy	3	0	100
Nechima	2.7	0.1	96
Orangina	1	0.2	80
Cameo	6.2	1.4	77
Cinnamon Buns	8	3.4	58
Chester	4.1	2.2	46
Lucky	2.6	1.6	39
Judd	6.9	4.7	32
Petey	5.2	7.1	−37
Mean	4.4	2.3	54.7
S.E.	0.8	0.8	14.0

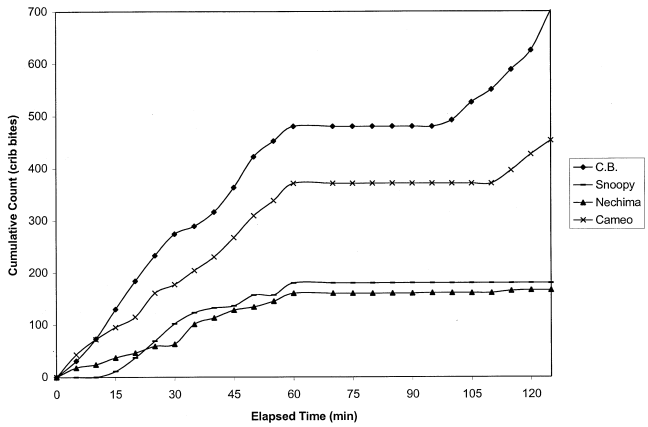

Fig. 1. Temporary abolition of cribbing in four horses following the intravenous injection of DM. The first period represents the cumulative control CR of the horses (expressed every 5-min time period) following intravenous injection of 10-ml saline. At 60 min, 1-mg/kg DM was injected intravenously, and the cumulative CR was recorded for an additional 60 min.

% Maximum efficacy scores of the nine horses treated with DM ranged from 100% to −37% (mean ± S.E. = 54.7 ± 14.0%; Table 2). One horse stopped cribbing for the entire 60-min period following injection of DM (Fig. 1) but resumed cribbing at what appeared to be close to the original CR in a short while after the test period. Three horses stopped cribbing completely for a period of time (35, 50, and 50 min, respectively) following treatment with DM (Fig. 1). Four horses showed an overall reduction in CR though the cribbing behavior did not stop completely for more than a few minutes at a time (Fig. 2). Only one horse showed a higher CR after DM than before, earning a % maximum efficacy of −37% (Table 2 and Fig. 2).

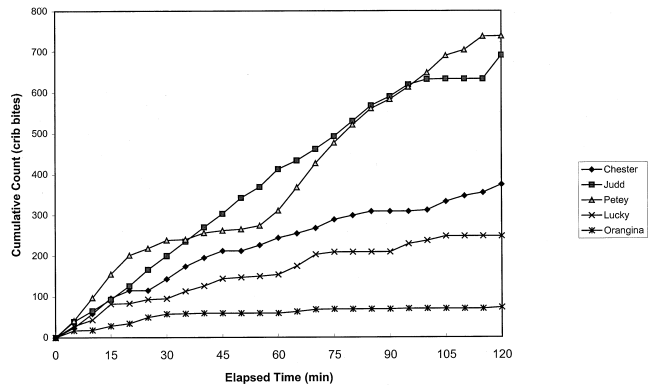

Fig. 2. Effect of saline and intravenous DM on cribbing in five horses that responded partially (four horses) or not at all (one horse) during the drug phase of the trial. The first period represents the cumulative control CR of the horses (expressed every 5-min time period) following intravenous injection of 10-ml saline. At 60 min, 1-mg/kg DM was injected intravenously, and the cumulative CR was recorded for an additional 60 min.

4. Discussion

There is evidence that high levels of dopaminergic activity within the basal ganglia play an important role in many stereotypies (Dodman, 1998). Dopaminergic activity is modulated by many neurotransmitters including endogenous opioids and glutamate (Livezey et al., 1995; Luescher, 1998). One theory for the mechanism underlying the development of stereotypies including cribbing in horses is that stress causes release of β-endorphin in the brain, stimulating dopamine release in the striatum and activating basal ganglia motor programs (Dodman et al., 1987). Behaviors that accompany stress could be reinforced through these pathways, becoming fixed in action. In support of this theory, a recent study found the plasma level of β-endorphin in cribbing horses to be three times greater than that of controls (Lebelt et al., 1998). Additionally, stereotypic behaviors elicited by the administration of exogenous opioids such as morphine have been demonstrated to depend on dopaminergic pathways (Pollock and Kornetsky, 1989; Shuster et al., 1984). Adding to an already complex picture, there is evidence that the opioids may be acting on dopaminergic neurons indirectly through NMDA receptors. An increase of extracellular dopamine in the striatum of rats caused by infusions of an opioid receptor agonist was completely blocked by co-administration of NMDA receptor antagonists. Kainate and AMPA receptor antagonists had no effect (Dourmap and Costentin, 1994).

Though DM blocks NMDA receptors, partial stimulation of dopamine release may still occur through the release of opioids during a cribbing event. Co-stimulation of receptors facilitating dopamine release might account for the observation that DM did not produce a complete cessation of cribbing in the majority of horses tested. This possibility could be tested by administering low levels of opioid and NMDA receptor blockers together to determine whether they produce a synergistic effect. Alternatively, NMDA receptors play a more active role during the development of a compulsive behavior than during the maintenance of a long established behavior. The role of NMDA receptors in learning and memory is well known. Certain forms of long-term potentiation have been shown to depend on activation of NMDA receptors in the hippocampus, a brain region important in memory (Kandel, 1991). Treating established compulsions with NMDA receptor blockers may be targeting this pathway too late but might be more effective in treating younger horses that are just acquiring the behavior.

The present study was intended as an efficacy study to investigate the putative involvement of NMDA receptor activation in compulsive cribbing behavior. The results suggest that targeting the NMDA receptor pathway to treat this ubiquitous equine behavior problem may prove to be a fruitful therapeutic strategy. Further work in the form of dose ranging and pharmacokinetic studies with DM as well as acute and chronic toxicity studies in experimental horses are necessary before therapeutic recommendations can be made. However, it seems likely that DM administration in conjunction with environmental enrichment and behavioral modification may well provide an effective treatment for cribbing in horses.

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